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ORIGINAL ARTICLE

Oleuropein attenuates the progression of heart failure in rats by antioxidant and antiinflammatory effects

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Abstract Much of the beneficial effects of olive products have been attributed to oleuropein. This study examined the effects of oleuropein in rats with heart failure induced by permanent ligation of left coronary arteries. Twenty-four hours after the operation, the rats were assigned to five groups including a sham assigned to receive vehicle (1 ml/day) and four coronary ligated groups assigned to receive vehicle or oleuropein at 5, 10, or 20 mg/kg/day. Five weeks later, echocardiographic and hemodynamic parameters, serum concentrations of oxidative stress, and inflammatory markers were determined. Myocardial infarction group receiving vehicle showed impaired hemodynamic and echocardiographic parameters as evidenced by decreased left ventricular systolic pressure, rate of rise and decrease of left ventricular pressure, stroke volume, ejection fraction, and cardiac output. In addition, significant reduction in superoxide dismutase and glutathione reductase was observed. Oleuropein treatment prevented the reduction of these variables. Moreover, the group had a significantly higher infarct size and serum malondialdehyde, interleukin-1β, and tumor necrosis factor-α than those of the sham group. Treatment with oleuropein prevented the increase of these variables. The results show that oleuropein attenuates the progression of heart failure, possibly by antioxidative and antiinflammatory effects.

Keywords Heart failure · Inflammatory cytokines · Oleuropein · Oxidative stress · Rat

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Introduction

Heart failure, the inability to pump blood to meet the body's demand, is one of the most common causes of cardiovascular morbidity and mortality, and its prevalence is rapidly increasing (Gandhi et al. 2001; Sola et al. 2006). The most common cause of heart failure is myocardial infarction, which initiates a cascade of progressive structural and geometric changes in the left ventricle leading to progressive inability of the heart to maintain cardiac output.

Human and experimental models of heart failure are associated with hemodynamic and echocardiographic changes including progressive left ventricular dilation and increased left ventricular end-diastolic pressure (LVEDP) (Mercanoglu et al. 2010; Parveen et al. 2011; Radovanovic et al. 2012). They are also associated with decreased stroke volume (SV), fractional shortening (FS), ejection fraction (EF), cardiac output (CO), rate of rise of left ventricular pressure (+dp/dt), and rate of decrease of left ventricular pressure (−dp/dt) (Mercanoglu et al. 2010; Parveen et al. 2011; Radovanovic et al. 2012).

The pathogenesis and progression of heart failure have been attributed to increased reactive oxygen species

(Giordano 2005) and lipid peroxidation markers like malondialdehyde (MDA). It has also been attributed to decreased antioxidant defenses like superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) (Li et al. 2012). Moreover, it has been related to increased proinflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) (Ertl and Frantz 2005; Nian et al. 2004).

It has been reported that coronary heart disease, a major contributor to heart failure, is not a major indicator of mortality in men living in areas where Mediterranean diets constitute the major portions of their diets (Menotti et al. 1997). Olive products constitute a major portion of Mediterranean diet (Huang and Sumpio 2008). Much of the beneficial effects of Mediterranean diets have been attributed to polyphenol compounds (Andreadou et al. 2006; Huang and Sumpio 2008; Keys 1980; Manna et al. 2004). A strong correlation has been shown between the intake of foods rich in such compounds and low mortality due to coronary heart disease (Andreadou et al. 2006; Huang and Sumpio 2008; Keys 1980; Manna et al. 2004). Oleuropein, an important polyphenol of olive products, has been reported to have beneficial effects such as cardioprotective, antioxidant (Andreadou et al. 2006; Manna et al. 2004), antiinflammatory (Kim et al. 2010), antiplatelet (Omar 2010), and vasodilatory (Omar 2010). Moreover, we (Janahmadi et al., 2015) previously showed that pretreatment with oleuropein for 1 week prior to ligation of the coronary artery offered cardioprotection in the setting of acute myocardial infarction.

Given the beneficial effects of oleuropein, the present study was designed to examine the effects of oleuropein on the progression of rat model of heart failure induced by permanent ligation of the coronary artery. It also aimed to examine whether oleuropein's effects were mediated by antioxidant and antiinflammatory activities.

Materials and methods

Animals

Male Sprague-Dawley rats (200–250 g) were obtained from Laboratory Animal Breeding Centre, Shiraz University of Medical Sciences, Shiraz, Iran. They were maintained under standard conditions (12-h light/dark cycle at 20–24 °C and 25–35% humidity) with standard rat chow and water ad libitum.

Materials

Oleuropein was purchased from Serva (Feinbiochemica, Heidelberg, Germany). Ketamine was obtained from Rotexmedica (Trittau, Germany) and xylazine from Alfasan (Woerden, Holland). Thiobutabarbital (Inactin®) was bought from ByK Gulden (Konstanz, Germany).

Surgical procedures

Animals were anesthetized with intraperitoneal injections of ketamine (60 mg/kg) and xylazine (8 mg/kg). They were then tracheally intubated and ventilated by a rodent respirator (Ugo Basile, Comerio, Italy) with room air at a frequency of 70 strokes/min and tidal volume of 1 ml/100 g body weight. Body temperature was maintained at 37 ± 1 °C using a temperature controller (Physitemp Instruments, Clifton, USA) by means of a rectal probe. The chest cavity was opened at the level of left fourth intercostal space, and the hearts were exposed. The pericardial sacs were then opened, and left main coronary arteries were ligated at 2–4 mm from their origins using 5-0 prolene. In sham-operated rats, the sutures were passed around the coronary arteries but were not tightened. Afterwards, the chest walls and skin incisions were closed using absorbable and nonabsorbable suture materials, respectively (Janahmadi et al. 2015). The animals were then recovered from anesthesia and kept in single cages under standard conditions for 5 weeks, during which they were given daily vehicle (1 ml distilled water), or oleuropein by oral gavage.

Experimental design

Starting from the next day after the operation, two groups including a sham-operated group assigned to receive vehicle (Sham-V) and a coronary artery-ligated group emerged. The coronary artery-ligated group was further randomly divided into four groups (n = 6–8) including a group assigned to receive vehicle (CAL-V) and three other groups assigned to receive oleuropein at 5 mg/kg/day (CAL-Ole5), 10 mg/kg/day (CAL-Ole10), or 20 mg/kg/day (CAL-Ole20).

Hemodynamic measurements

After 5 weeks of treatment with vehicle of oleuropein, the animals were anesthetized with single intraperitoneal injections of thiobutabarbital (100 mg/kg). Heparinized saline-filled catheters were inserted into left carotid arteries for the measurement of systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). Moreover, catheters were placed in right carotid arteries and advanced to left ventricles for the measurement of left ventricular systolic pressure (LVSP), LVEDP, and left ventricular +dp/dt and −dp/dt. The animals were allowed to recover from surgical stress for 30 min, and then, measurements of the hemodynamic variables were performed using a PowerLab data acquisition system (ML750, ADInstruments PowerLab System, Castle Hill, Australia).

Echocardiographic measurements

After the measurement of hemodynamic variables, the animals were subjected to transthoracic echocardiography using a 10-5-MHz probe (Esaote, Florence, Italy). Two-dimensional guided M-mode images of the left ventricle were obtained from the short axis view at the level of papillary muscle. Left ventricular internal diameter in diastole (LVIDd) and left ventricular internal diameter in systole (LVIDs) were measured, and diastolic and diastolic volumes, SV, FS, EF, and CO were calculated (see in the following).

After the measurement of echocardiographic variables, blood samples were obtained and allowed to clot for 30 min. The blood samples were then centrifuged at 1000*g* for 20 min, and their serums were separated and stored at −80 °C until analysis.

Assessment of infarct size

Cardiac infarct size was assessed as previously described (Srikanth et al. 2009). The hearts were excised and washed in ice-cold 0.9% saline and were embedded into parafilm. After being kept at −4 °C for 1 h, they were cut transversely into 2-mm-thick slices. The slices were then incubated with 1% TTC at 37 °C for 25 min. The stained slices were fixed with 10% formaldehyde overnight. The infarct sizes were determined via planimetry by using the NIH image software.

Measurements of serum biomarkers

Serum MDA (Bioassay Technology Laboratory, Shanghai, China), TNF-α (Glory Science, Del Rio, TX, USA), and IL-1β (Boster Biological Technology, Wuhan, China) levels were measured by the ELISA method using the manufacturers' instructions. Serum SOD and glutathione reductase (GRx) were measured using chemical kits (Biorexfars, Shiraz, Iran).

Calculations

Mean arterial pressure (MAP) was calculated as DBP plus one third of arterial pulse pressure. Arterial resistance (AR) was calculated as MAP/CO. Diastolic and systolic volumes were calculated as $1.047[\text{LVIDd}]^3$ and $1.047[\text{LVIDs}]^3$, respectively. SV was calculated as diastolic volume − systolic volume. FS was calculated as [LVIDd − LVIDs] / LVIDd). EF was calculated as stroke volume / diastolic volume and CO as SV × HR.

Statistical analysis

Data, presented as mean ± SEM, were analyzed using one-way analysis of variance (ANOVA) followed by Duncan's multiple range test for pairwise comparisons. A P value of ≤ 0.05 was considered statistically significant. The data were analyzed using SigmaStat Statistical Software version 3.0 (San Jose, CA, USA). The illustrations were drawn using the SigmaPlot software (version 8.0) (San Jose, CA, USA).

Results

Hemodynamic variables

SBP, LVSP, +dp/dt, and −dp/dt of the CAL-V group were significantly lower than those of the Sham-V group. However, AR and LVEDP of that group were significantly higher than those of the Sham-V group (Table 1).

There were no significant differences between the SBP, LVSP, +dp/dt, −dp/dt, or LVEDP of CAL-Ole5 and CAL-V groups. However, SBP, LVSP, +dp/dt, and −dp/dt of CAL-Ole10 and CAL-Ole20 groups were significantly higher than those of the CAL-V group, while AR and LVEDPs of such groups were significantly lower than those of the CAL-V group. There was no significant difference between the DBP, MAP, or HR of Sham-V, CAL-V, CAL-Ole5, CAL-Ole10, and CAL-Ole20 groups (Table 1).

Echocardiographic variables

The LVIDs, LVIDd, systolic volume, and diastolic volume of the CAL-V group were significantly higher than those of the Sham-V group. However, SV, EF, FS, and CO of the CAL-V group were significantly lower than those of the Sham-V group. There were no significant differences between the LVIDs, LVIDd, systolic and diastolic volumes, SV, EF, FS, and CO of CAL-Ole5 and CAL-V groups. The LVIDs, LVIDd, systolic volume, and diastolic volume of CAL-Ole10 and CAL-Ole20 groups were significantly lower than those of the CAL-V group. However, the SV, EF, FS, and CO of CAL-Ole10 and CAL-Ole20 groups were significantly higher than those of the CAL-V group (Table 2 and Fig. 1).

Infarct size

There was no significant difference between the infarct size of CAL-Ole5 and CAL-V groups (Fig. 2). The infarct sizes of CAL-Ole10 and CAL-Ole20 groups were significantly lower than those of the CAL-V group.

Serum biomarkers

Serum levels of SOD and GRx of the CAL-V group were significantly lower than those of the Sham-V group (Fig. 3). There was no significant difference between the serum concentrations of SOD or GRx of CAL-V and CAL-Ole5 groups.

Table 1 The values of hemodynamic parameters of all experimental groups

	Sham-V	CAL-V	CAL-Ole5	CAL-Ole10	CAL-Ole20
SBP (mmHg)	125.5 ± 2.35	110.8 ± 2.4†	116.1 ± 2.9	119.7 ± 2.1‡	122.4 ± 2.4‡
DBP (mmHg)	93.4 ± 2.5	88.9 ± 2.6	95.5 ± 2.7	94.3 ± 3.1	98.9 ± 2.4
MAP (mmHg)	104.3 ± 1.9	97.9 ± 2.4	102.1 ± 2.5	103.7 ± 2.5	106.2 ± 2.2
AR (mmHg/ml)	1.128 ± 0.087	1.579 ± 0.077†	1.268 ± 0.037‡	1.196 ± 0.116‡	1.190 ± 0.082‡
HR (beats/min)	411.9 ± 8.2	391.3 ± 11.7	396.1 ± 10.1	419.5 ± 10.8	399.2 ± 11.4
LVSP (mmHg)	134.3 ± 1.7	111.8 ± 2.7†	117.3 ± 2.6	124.9 ± 1.8‡	127.2 ± 1.5‡
LVEDP (mmHg)	−2.8 ± 0.2	4.5 ± 0.4†	3.7 ± 0.3	−0.2 ± 0.3‡	−2.5 ± 0.1‡
+dp/dt (mmHg/s)	5246 ± 212	3688 ± 115†	3803 ± 119	4474 ± 104‡	5285 ± 87‡
−dp/dt (mmHg/s)	−4398 ± 181	−2952 ± 81†	−3204 ± 76	−3605 ± 114‡	−4153 ± 86‡

Data are shown as mean ± SEM, n = 6–8 each group

SBP systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure, *AR* arterial resistance, *HR* heart rate, *LVSP* left ventricular systolic pressure, *LVEDP* left ventricular end-diastolic pressure, *+dp/dt* rate of rise of left ventricular pressure, *−dp/dt* rate of decrease of left ventricular pressure, *Sham-V* sham group receiving vehicle (1 ml distilled water/day), *CAL-V* coronary artery-ligated group receiving vehicle, *CAL-Ole5* coronary artery-ligated group receiving oleuropein at 5 mg/kg/day, *CAL-Ole10* coronary artery-ligated group receiving oleuropein at 10 mg/kg/day, *CAL-Ole20* coronary artery-ligated group receiving oleuropein at 20 mg/kg/day

†Significant ($p \leq 0.05$) difference from the Sham-V group; ‡Significant ($p \leq 0.05$) difference from the CAL-V group

The serum concentrations of SOD and GRx of CAL-Ole10 and CAL-Ole20 groups were significantly higher than those of the CAL-V group (Fig. 3).

Serum level of MDA of the CAL-V group was significantly higher than that of the Sham-V group (Fig. 3). There was no significant difference between the serum concentrations of MDA of CAL-V and CAL-Ole5 groups. Serum MDA concentration of CAL-Ole10 and CAL-Ole20 groups was significantly lower than that of the CAL-V group (Fig. 3).

Serum levels of IL-1β and TNF-α of the CAL-V group were significantly higher than those of the Sham-V group (Fig. 4). There was no significant difference between serum concentrations of IL-1β or TNF-α of CAL-V and CAL-Ole5 groups. Serum concentrations of IL-1β or TNF-α of CAL-Ole10 and CAL-Ole20 groups were significantly lower than those of the CAL-V group (Fig. 4).

Discussion

The findings of the present study show that permanent ligation of left main coronary results in heart failure and that oleuropein offers cardioprotection in rats with heart failure They also show that cardioprotection offered by oleuropein

Table 2 The values of echocardiographic parameters of all experimental groups

	Sham-V	CAL-V	CAL-Ole5	CAL-Ole10	CAL-Ole20
LVIDs (cm)	0.32 ± 0.02	0.80 ± 0.03†	0.79 ± 0.04	0.66 ± 0.04‡	0.69 ± 0.02‡
LVIDd (cm)	0.64 ± 0.02	0.87 ± 0.02†	0.89 ± 0.03	0.79 ± 0.037	0.82 ± 0.02
SYS VOL (ml)	0.036 ± 0.01	0.54 ± 0.05†	0.53 ± 0.08	0.32 ± 0.06‡	0.34 ± 0.03‡
DIA VOL (ml)	0.28 ± 0.03	0.70 ± 0.05†	0.75 ± 0.08	0.54 ± 0.08	0.58 ± 0.03
SV (ml)	0.24 ± 0.02	0.17 ± 0.01†	0.21 ± 0.01	0.22 ± 0.02‡	0.24 ± 0.01‡
EF (%)	87.1 ± 1.9	23.7 ± 1.7†	30.18 ± 2.9	42.3 ± 3.1‡	41.7 ± 2.5‡
FS (%)	50.4 ± 2.8	8.7 ± 0.7†	11.4 ± 1.2	16.9 ± 1.6‡	16.4 ± 1.1‡
CO (ml/min)	95.7 ± 7.5	63.4 ± 3.1†	81.0 ± 3.2	91.1 ± 9.6‡	93.8 ± 6.3‡

Data are shown as mean ± SEM, n = 6–8 each group

LVIDs left ventricular internal diameter in systole, *LVIDd* left ventricular internal diameter in diastole, *SYS VOL* systolic volume, *DIA VOL* diastolic volume, *SV* stroke volume, *EF* ejection fraction, *FS* fractional shortening, *CO* cardiac output, *Sham-V* sham-operated group receiving vehicle (1 ml distilled water/day), *CAL-V* coronary artery-ligated group receiving vehicle, *CAL-Ole5* coronary artery-ligated group receiving oleuropein at 5 mg/kg/day, *CAL-Ole10* coronary artery-ligated group receiving oleuropein at 10 mg/kg/day, *CAL-Ole20* coronary artery-ligated group receiving oleuropein at 20 mg/kg/day

†Significant ($p \leq 0.05$) difference from the Sham-V group; ‡significant ($p \leq 0.05$) difference from the CAL-V group

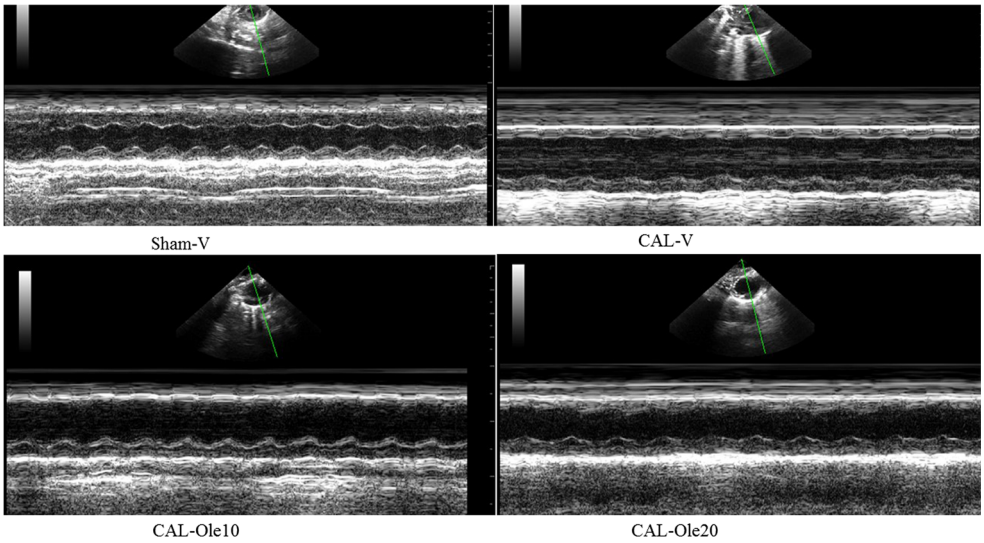

Fig. 1 Representative echocardiography photographs. Two-dimensional, *upper plane*, and M-mode, *lower plane*, short-axis views of left ventricle at the level of papillary muscles of all experimental groups. *Sham-V* sham-operated group receiving vehicle (1 ml distilled water/day), *CAL-V* coronary artery-ligated group receiving the vehicle, *CAL-Ole10* coronary artery-ligated group receiving oleuropein at 10 mg/kg/day, *CAL-Ole20* coronary artery-ligated group receiving oleuropein at 20 mg/kg/day

might be related to the oleuropein's amelioration of oxidative stress and release of proinflammatory cytokines.

In a previous study (Janahmadi et al. 2015), we showed that oleuropein, given as pretreatment for 1 week prior to ligation of the coronary artery, was able to offer protection against acute myocardial infarction. The study showed that oleuropein cardioprotection might be mediated by reduction of oxidative stress and proinflammatory cytokines. The present study aimed to examine the treatment effects of oleuropein on the progression of heart failure. The hemodynamic and echocardiographic findings of the present study show that permanent ligation of the coronary artery for 5 weeks results in heart failure. Our study shows that cardiac hemodynamic parameters including LVSP, +dp/dt, and −dp/dt were significantly lower, and LVEDP was higher in coronary artery-ligated group receiving vehicle than in sham-operated group. Such findings are similar to those of previous studies using the same model (Huang et al. 2009) or other models (Garjani et al. 2011) of experimental as well as human (Aurigemma et al. 2006) heart failure. Moreover, echocardiographic assessments showed that LVIDs, LVIDd, systolic volume, and diastolic volume of coronary artery-ligated rats receiving vehicle were significantly higher, while SV, EF, FS, and CO of that group were significantly lower than those of the sham-operated group. The echocardiographic findings are similar to those of earlier studies on experimental (Huang et al. 2009; Mercanoglu et al. 2010; Zhang et al. 2014; Zhou et al. 2007) and clinical (Radovanovic et al. 2012) heart failure.

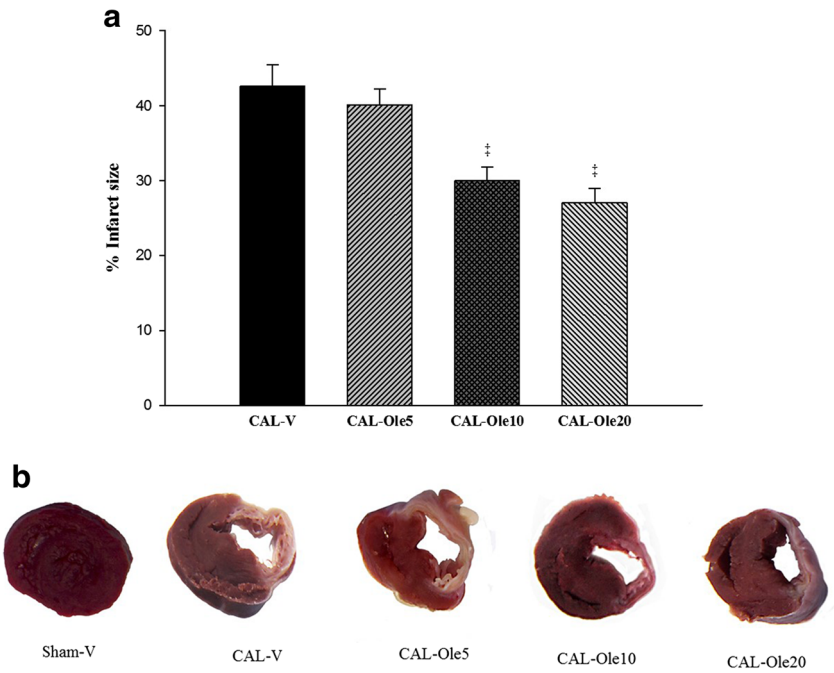

Fig. 2 **a** Infarct size (as a percentage of the left ventricle) of coronary artery-ligated groups and **b** representative photographs of myocardial slices from sham-operated and coronary artery-ligated groups. *Sham-V* sham group receiving vehicle (1 ml distilled water/day), *CAL-V* coronary artery-ligated group receiving vehicle (1 ml distilled water/day), *CAL-Ole-5* coronary artery-ligated group receiving oleuropein at 5 mg/kg/day, *CAL-Ole10* coronary artery-ligated group receiving oleuropein at 10 mg/kg/day, *CAL-Ole20* coronary artery-ligated group receiving oleuropein at 20 mg/kg/day. Data are shown as mean ± SEM, $n = 6–8$ each group. ‡Significant difference ($p \leq 0.05$) from CAL-V

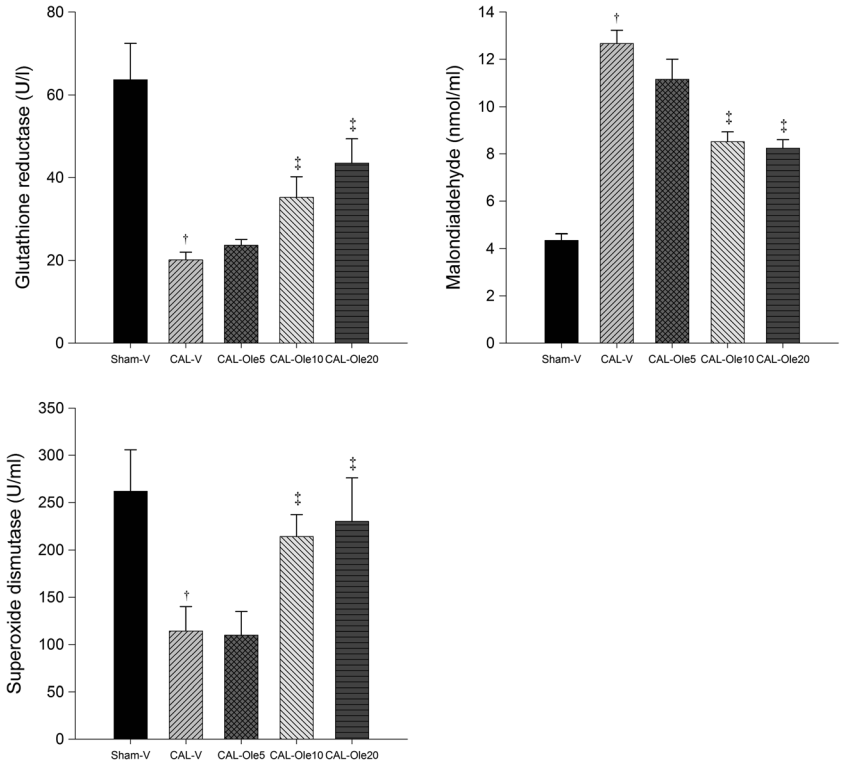

Fig. 3 Serum levels of biomarkers of oxidative stress of all experimental groups. *Sham-V* sham-operated group receiving vehicle (1 ml distilled water/day), *CAL-V* coronary artery-ligated group receiving vehicle, *CAL-Ole-5* coronary artery-ligated group receiving oleuropein at 5 mg/kg/day, *CAL-Ole10* coronary artery-ligated group receiving oleuropein at 10 mg/kg/day, *CAL-Ole20* coronary artery-ligated group receiving oleuropein at 20 mg/kg/day. Data are shown as mean ± SEM, $n = 6$–8 each group. †Significant difference ($p \leq 0.05$) from Sham-V. ‡Significant difference ($p \leq 0.05$) from CAL-V

The progressive worsening of heart failure has been attributed to a number of mechanisms including the increase of oxidative stress (Giordano 2005), release of proinflammatory cytokines (Bozkurt et al. 2010), and neurohormonal activation (McAlpine et al. 1988). We, therefore, measured the serum concentrations of indices of oxidative stress such as SOD, GRx and MDA and proinflammatory cytokines such as IL-1β and TNF-α. Serum concentration of markers of oxidative stress and proinflammatory cytokines can predict the severity of heart failure as they were correlated with the severity of it (Wojciechowska et al. 2014; Zarrouk-Mahjoub et al. 2016). Our findings show that the present model of heart failure is associated with increased oxidative stress and release of proinflammatory cytokines. It has been suggested that oxidative stress via numerous mechanisms such as direct cytotoxic and negative inotropic (Ferrari et al. 1998), cytokine-stimulating (Mak and Newton 2001), and apoptotic (Kumar et al. 2002) effects contributes to the development of heart failure. Moreover, the contribution of proinflammatory cytokines to the development of the disease has been related to their ability to directly affect cardiac structure and contractile function (Hegewisch et al. 1990; Klug et al. 1993).

Oleuropein, at two largest doses of 10 and 20 mg/kg/day, attenuated the decrease of SBP, LVSP, +dp/dt, and −dp/dt and

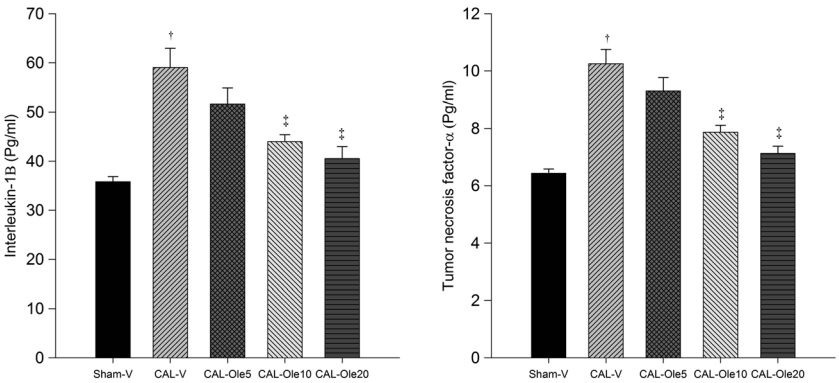

Fig. 4 Serum levels of proinflammatory cytokines of all experimental groups. *Sham-V* sham-operated group receiving vehicle (1 ml distilled water/day), *CAL-V* coronary artery-ligated group receiving vehicle, *CAL-Ole5* coronary artery-ligated group receiving oleuropein at 5 mg/kg/day, *CAL-Ole10* coronary artery-ligated group receiving oleuropein at 10 mg/kg/day, *CAL-Ole20* coronary artery-ligated group receiving oleuropein at 20 mg/kg/day. Data are shown as mean ± SEM, $n = 6$–8 each group. †Significant difference ($p \leq 0.05$) from Sham-V. ‡Significant difference ($p \leq 0.05$) from CAL-V

the increase of LVEDP and infarct size in coronary artery-ligated rats. It also prevented the increase of LVIDs, LVIDd, systolic volume, and diastolic volume and the decrease of SV, EF, FS, and CO in such rats. These findings show that oleuropein at the two latter doses has cardioprotective effects. Such a conclusion receives support from previous studies demonstrating that oleuropein was cardioprotective against acute and chronic doxorubicin-induced cardiotoxicities (Andreadou et al. 2014; Andreadou et al. 2007) and ischemia-reperfusion injuries (Andreadou et al. 2006).

The cardioprotective effects of oleuropein have been attributed to several mechanisms such as reduction of oxidative and nitrosative stress (Andreadou et al. 2007) as well as antiplatelet (Petroni et al. 1995), hypolipidemic (Andreadou et al. 2006), and antiinflammatory (Andreadou et al. 2014) activities. We, therefore, sought to measure serum levels of SOD, GRx, MDA, IL-1β, and TNF-α to examine the role of oxidative stress and proinflammatory cytokines in the oleuropein's cardioprotective effects. Our findings show that oleuropein reduces proinflammatory cytokines and increased antioxidant markers. Such findings are similar to those that reported that oleuropein reduced prooxidants and proinflammatory cytokines and increased antioxidant markers in adriamycin cardiotoxicity (Andreadou et al. 2014; Andreadou et al. 2007) and myocardial ischemia/reperfusion (Andreadou et al. 2006; Manna et al. 2004) studies.

Hemodynamically speaking, part of the beneficial effects of oleuropein might be related to its hypotensive and vasodilatory effects. We (Nekooeian et al. 2014) and others (Romero et al. 2016; Zarzuelo et al. 1991) showed that oleuropein possessed hypotensive and vasodilatory effects. It is interesting that, nonetheless, treatment with oleuropein was associated with increased SBP in the present model of heart failure, which was associated with reduced SBP and increased AR. The possible explanation for such an effect is that oleuropein, by virtue of its vasodilating activity, reduced AR and afterload. The reduced afterload may have helped that failing heart to function effectively and increase CO and consequently SBP. This explanation is in agreement with the most recent guidelines on the effectiveness of the use of vasodilators in the management of human heart failure (Yancy et al. 2013).

Taken together, our findings receive support from and give support to the widely accepted belief that Mediterranean diets, by virtue of richness in olive products, are associated with lower morbidity and mortality due to coronary heart diseases (Keys 1997). Given the role of coronary heart diseases in the initiation and progression of heart failure, our findings may be of clinical and practical relevance. Our findings may lay the ground for subsequent studies of oleuropein in other animal models of the disease and human heart failure and future use of the compound in the setting of human heart failure.

One limitation of the present study was the absence of a group of sham-operated rats receiving oleuropein diet. The presence of such a group could provide a chance to compare the effects of oleuropein in sham-operated and heart failure rats.

In conclusion, the findings of the present study indicate that oleuropein is cardioprotective in rats with heart failure, and such an effect might be mediated by antioxidant and antiinflammatory activities.

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Compliance with ethical standards All procedures were approved by the Institutional Committee for Ethics, Care, and Use of Animals.

Conflict of interest The authors declare that they have no conflict of interest.

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